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ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,298	BERGMANN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/7/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,16,19-22,25,31,35-37,40,41,45-49,51,55,58,60-63 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,16,19-22,25,31,35-37,40,41,45-49,51,55,58,60-63 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 12/7/2010, is acknowledged and has been entered. Claims 2-3, 10, 19, 35, and 51 were amended. Claims 13-14, 18, 23-24, 26-30, 32-34, 38-39, 42-44, 50, 52-54, 56-57, 59, 64-67, and 69-70 were canceled. Accordingly, claims 1-11, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 51, 55, 58, 60-63, and 68 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

2. The objection to the specification containing new matter has been withdrawn in response to Applicant's amendments.

3. The rejections of claims 23, 32-34, 38, and 43 under § 112, 1st paragraph (written description) are moot in light of Applicant's cancellation of these claims.

4. The rejections of claims 24, 26-29, 39, 42, 51, 56, 64, and 69 under § 112, 1st paragraph (scope of enablement) are also moot in view of Applicant's cancellation of these claims.

5. The rejection of claim 16 under § 112, 1st paragraph (scope of enablement) is withdrawn in response to Applicant's persuasive arguments (see pages 11-12) and upon further consideration by the examiner, as this claim does not clearly require or invoke diagnosis or prognosis of a disease.

6. The rejections of claims 23, 26-29, 34, and 38 under § 112, 2nd paragraph are moot in view of Applicant's cancellation of these claims.

7. The rejections of claims 23, 32-33, 43-44, 52-53, 57, 65-66, and 70 under § 102 are moot in view of Applicant's cancellation of these claims.

8. The rejections of claims 23 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Kennedy et al. and further in view of Bergmann et al. (WO 00/22439) are moot in view of Applicant's cancellation of these claims.

9. The rejections of claims 34, 54, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Kennedy et al. are moot in view of Applicant's cancellation of these claims.

Information Disclosure Statement

10. Applicant's Information Disclosure Statement filed 12/7/2010 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449/ PTO/SB/08a.

The non-patent literature publications by **Pio et al.** and **Lewis et al.** have been lined through to avoid duplicate citation, as they were previously cited on Applicant's IDS of 7/24/2006. The references have been considered by the examiner (see signed copy of the IDS as attached to the Office action mailed 3/27/2008).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-9, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 51, 55, 58, 60-63, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 53, 60-61, 72-76, 555, 559, 561, and 578-579) in view of Kennedy et al. ("Expression of the Rat Adrenomedullin Receptor or a Putative Human Adrenomedullin Receptor Does Not Correlate with Adrenomedullin Binding or Functional Response" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 244, 832–837 (1998).

Harlow & Lane teach that to detect and quantitate antigens, the most useful method is the two antibody sandwich assay. This assay employs either two monoclonal antibodies that bind to independent sites on the antigen or alternatively, affinity-purified antibodies. See pages 555, 559, 561, and 578-579. More particularly, a fluid sample is applied to a solid phase upon which a first antibody is bound, allowing the antigen to bind to the antibody. Next, a second labeled antibody is bound to the antigen and the label is detected, allowing the antigen to be quantified. See pages 578-580.

Harlow & Lane therefore teach a method for measuring the level of an antigen in a fluid sample, in which the measuring uses a monoclonal or polyclonal antibody that is specific to the antigen being determined.

Harlow & Lane is generic with respect to the antigen being determined, and does not teach the antigen mid-proAM (SEQ ID NO:3).

Kennedy et al. teach that preproadrenomedullin is a 185-amino acid molecule that is processed into adrenomedullin as well as other biologically active peptides, including the peptide corresponding to amino acids 45-92 of preproadrenomedullin. See page 832, left column.

Kennedy et al. further teach that there clearly exists a need for defining the specific role of adrenomedullin and its related peptides in normal and pathological states (page 832, right column).

The teachings of Kennedy et al. indicate that the peptide corresponding to amino acids 45-92 of preproadrenomedullin (i.e., mid-proAM or SEQ ID NO:3) was known in the art to exist and to be a biologically active peptide that is related to adrenomedullin. Kennedy et al. also call for studies to define the specific role of this peptide.

It would have been obvious to one of ordinary skill in the art to employ the assay methods of Harlow & Lane in order to detect and quantitate mid-proAM in the course of carrying out studies to define the specific role of this peptide, as suggested by Kennedy et al. For example, as Kennedy et al. discuss the possible role of adrenomedullin and its related peptides (including mid-proAM) in normal and pathological states, it would have been obvious to detect and quantify these molecules in samples taken from normal individuals and individuals known to have disease in order to investigate the possible role of mid-proAM in disease.

With respect to claim 22, Kennedy et al. teaches that adrenomedullin circulates in plasma (see page 832). When taken together with the teaching that both mid-proAM and adrenomedullin are processed from the same larger precursor molecule (preproadrenomedullin), it would have been obvious to also conduct the methods of Harlow & Lane and Kennedy et al. on plasma samples since mid-proAM would also be likely to be found in plasma.

With respect to claim 16, it is noted that the claim refers to cardiac diagnosis but does not include any active method steps in which disease is actually diagnosed, for example. As such, the reference to such clinical goals may be reasonably interpreted as being directed only to a possible intended use or downstream use of the claimed method. For these reasons, the teachings of Harlow & Lane and Kennedy et al. read on the claim. Notwithstanding the above, it is noted that Kennedy et al. also discuss the role of adrenomedullin in cardiac disease (paragraph bridging the left and right columns of page 832). As such, it would have been obvious to detect and quantify adrenomedullin and its related peptides (including mid-proAM) in order to investigate the possible role of mid-proAM as a marker for diagnosis of cardiac disease.

Regarding claim 5, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to arrive at the claimed invention by raising antibodies against C-terminal sequences of SEQ ID NO:3, since amino acids 60-94 correspond to the C-terminus of SEQ ID NO:3. It would have been obvious to do this according to routine laboratory procedures which suggest C-terminal sequences as being likely to produce antibodies that recognize the native protein.

Regarding claim 8, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies as detailed above. Therefore, it would have been further obvious to arrive at the claimed invention by produce the antibodies for the sandwich immunoassays using either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 per se "comprises" amino acids 68-86 and 83-92 of pre-proAM, antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, or bacterially expressed proteins.

13. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Kennedy et al. as applied to claim 3 above, and further in view of Mathis et al. ("Probing Molecular Interactions with Homogeneous Techniques Based on Rare Earth Cryptates and Fluorescence Energy Transfer" Clin. Chem. 41/9, 1391-1397 (1995)).

Harlow & Lane teach sandwich immunoassays that employ labeled antibodies, but fail to specifically teach that the labeling system is based on fluorescence or chemiluminescence extinction as claimed, or in particular a system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

Mathis et al. teach homogeneous immunoassay methods based on the use of rare earth cryptates as fluorescent labels (the abstract and page 1392). Such immunoassays involve two monoclonal antibodies raised against the antigen, which are labeled respectively with Eu^{3+} cryptate (rare earth cryptate) and with allophycocyanin (cyanine type fluorescent dye). See page 1392 and Figure 1 in particular.

Mathis et al. further teach that such homogeneous fluoroassays are free from media interactions, allowing for development of assays that involve only a minimal perturbation of equilibrium or steric environment (page 1395, "Discussion" to page 1396, left column).

Therefore, it would have been further obvious to one of ordinary skill in the art to modify the solid phase sandwich immunoassay of Harlow & Lane and Kennedy et al. so as to use the rare earth cryptate labeling system of Mathis et al. (which produce fluorescence emission) In

particular, it would have been obvious to label one of the antibodies in the sandwich assay of Harlow & Lane with Eu^{3+} cryptate and the other with allophycocyanin as taught by Mathis et al. in order to detect SEQ ID NO:3 in a homogeneous sandwich assay. Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect and quantitate SEQ ID NO:3 as taught by Harlow & Lane and Kennedy et al.

One would be motivated to do this in light of the teachings of Mathis et al. that the use of rare earth cryptates as fluorescent labels in immunoassays allows for homogeneous assays (i.e., no separation steps). Therefore, one would be motivated to perform a sandwich immunoassay for SEQ ID NO:3 using the labels of Mathis et al. so as to eliminate the need for separation or wash steps needed for typical ELISA procedures (such as that of Harlow & Lane). Furthermore, one would have been motivated to detect SEQ ID NO:3 by the homogeneous fluoroassay of Mathis et al. in order to allow for an assay that is free from media interactions.

One would have had a reasonable expectation of success because Mathis et al. also teaches that labeling of different types of molecules was done with ease (page 1395, "Discussion").

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The following are provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 55, 58, 60-63, and 68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 11/937061. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '061 application also claims a method of determining the level of pro-adrenomedullin or partial peptides or fragments thereof for in vitro diagnosis of patients post-myocardial infarction (see claim 1). The peptide fragment may be MR-proADM (see claims 2 and 19-20), which is the same peptide as the instantly recited SEQ ID NO:3 (see the specification of the '061 application at [006], which defines "MR-proADM as the peptide comprising amino acids 45-92 of preproADM). The '061 application also claims that additional markers can also be determined (i.e., multi-parameter determination). See claims 4-15.

16. Claims 1, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 55, 58, 60-63, and 68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable

over claims 1-13 of copending Application No. 12/374,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. 12/374,757 also claims a method in which the concentration of mid-proAM ("MR-proADM") is determined by sandwich immunoassay (see especially claims 1-4).

With respect to claims 27-29, which recite diagnosis of a disease other than sepsis, it is noted that the instant specification defines "diagnosis" so as to encompass monitoring of treatment (see [002] of the published application), which is the same purpose for which the method of the copending application is performed (see preamble of claim 1). In particular, Application No. 12/374,757 teaches a method for assessing changes in concentration due to treatment for cardiac insufficiency.

17. Claims 1, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 55, 58, 60-63, and 68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/305,088. Although the conflicting claims are not identical, they are not patentably distinct from each other because copending Application No. 12/305,088 also claims a method of determining the concentration of a midregional proADM fragment (MR-proADM) which comprises the amino acids 45-92 of pre-proadrenomedullin (i.e., mid-proAM). See in particular claims 1, 5, and 8. Biological fluid samples assayed may be blood, serum or plasma (claim 6). The method can be conducted using sandwich-type immunoassays (claim 10).

With respect to claims 27-29, Application No. 12/305,088 claims a method for detection or prognosis of neurodegenerative diseases.

18. Claims 2-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any one of: claims 1-20 of copending Application No. 11/937061; claims 1-13 of copending Application No. 12/305,088; or over claims 1-13 of copending Application No. 12/374,757 in view of Harlow & Lane.

The '088 and '757 applications recite a sandwich immunoassay (claims 4), but do not specifically mention that the assay uses a labeled analyte-specific antibody. The copending applications also fail to specifically recite that the antibodies for the sandwich immunoassay bind to a region on mid-proAM that extends from amino acids 60-94 of pre-proAM, or that the antibodies are obtained by immunization with the synthetic peptides recited in claim 8.

Harlow & Lane is as discussed above, which teaches laboratory procedures involving antibodies, including immunoassays. For example, the reference teaches that one of the most useful immunoassays is the two-antibody sandwich technique, which can be used to determine antigen concentration in a quick and accurate manner (pages 578-579). Such sandwich immunoassays require two antibodies that bind to non-overlapping epitopes on the antigen; either two monoclonal antibodies or one batch of affinity-purified polyclonal antibodies can be used (ibid). The first antibody is bound to a solid phase, while the second antibody is labeled (see diagram on the bottom of page 578, and page 579).

Harlow & Lane also teach that it is routine in the art to use synthetic peptides as immunogens in order to raise antibodies, and suggest carboxy-terminal sequences for designing such peptides since they are likely to be immunogenic and because a surprisingly high

percentage of antibodies raised using carboxy-terminal sequences will recognize the native protein. See pages 53, 60-61, and 72-76.

Regarding claims 2-3 and 9, it would have been obvious to arrive at the claimed invention by employing the sandwich immunoassay format of Harlow & Lane to detect MR-proADM in the methods of the copending applications. One would also be motivated to do this in light of the teachings of Harlow & Lane that sandwich immunoassays are one of the most useful immunoassays, being quick and accurate.

It would have been further obvious to select either monoclonal or affinity-purified polyclonal antibodies for such a sandwich immunoassay (as in claims 6-7) since Harlow & Lane taught that both of these produce excellent signal strength and specificity.

Regarding claim 5, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to arrive at the claimed invention by raising antibodies against C-terminal sequences of SEQ ID NO:3, since amino acids 60-94 correspond to the C-terminus of SEQ ID NO:3. It would have been obvious to do this according to routine laboratory procedures which suggest C-terminal sequences as being likely to produce antibodies that recognize the native protein.

Regarding claim 8, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies as detailed above. Therefore, it would have been further obvious to arrive at the claimed invention by produce the antibodies for the sandwich immunoassays using either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 per se "comprises" amino acids 68-86 and 83-92 of pre-proAM,

antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, or bacterially expressed proteins.

19. Claims 2-3, 6, and 10-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any one of: claims 1-20 of copending Application No. 11/937061; 1-13 of copending Application No. 12/305,088; or over claims 1-13 of copending Application No. 12/374,757 in view of Mathis et al. ("Probing Molecular Interactions with Homogeneous Techniques Based on Rare Earth Cryptates and Fluorescence Energy Transfer" Clin. Chem. 41/9, 1391-1397 (1995)).

The '757 and '088 applications recites sandwich immunoassays (claims 4), but do not specifically mention that the assay uses a labeled antibody. The copending applications also fail to recite an immunoassay that involves a labeling system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

Mathis et al. teach homogeneous immunoassay methods based on the use of rare earth cryptates as fluorescent labels (the abstract and page 1392). Such immunoassays involve two monoclonal antibodies raised against the antigen, which are labeled respectively with Eu^{3+} cryptate (rare earth cryptate) and with allophycocyanin (cyanine type fluorescent dye). See page 1392 and Figure 1 in particular.

Mathis et al. further teach that such homogeneous fluoroassays are free from media interactions, allowing for development of assays that involve only a minimal perturbation of equilibrium or steric environment (page 1395, "Discussion" to page 1396, left column).

In light of the teachings of Mathis et al., it would have been obvious to one of ordinary skill in the art to detect pro-adrenomedullin 45-92 (MR-proADM, SEQ ID NO:3) in the methods of the copending applications by the fluoroimmunoassay of Mathis et al. in the method of Bergmann et al. In particular, it would have been obvious to use two monoclonal antibodies against the antigen (i.e., pro-adrenomedullin 45-92) and to label one of the antibodies with Eu^{3+} cryptate (i.e., rare earth cryptate) and the other with allophycocyanin (i.e., fluorescent cyanine-type dye). Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect MR-proADM in the methods of the '250 or '061 applications. One would be motivated to do this in order to detect pro-adrenomedullin 45-92 in a homogeneous assay, requiring no separation steps. One would also be motivated to use the Mathis et al. fluoroimmunoassay in order to avoid the need to use radioactive labels.

20. Claims 1-9, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 51, 55, 58, 60-63, and 68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 12/514,194 and Harlow & Lane.

Application No. 12/514,194 also claims a method in which the concentration of mid-proAM ("MR-proADM") is determined (see especially claim 1). However, the copending application does not specifically recite that such a method uses an antibody.

However, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to employ the known two-antibody sandwich immunoassay format since this type of assay was recognized to be the most useful means of detecting and quantitating antigens.

21. Claims 10-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 12/514,194 and Harlow & Lane as applied to claim 3 above, and further in view of Mathis et al.

The copending application and Harlow & Lane fail to specifically teach that the labeling system is based on fluorescence or chemiluminescence extinction as claimed, or in particular a system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

However, in light of the teachings of Mathis et al. discussed in detail above, it would have been obvious to employ such a labeling system in order to avoid the need for separation or wash steps typically required in a sandwich immunoassay (such as that of Harlow & Lane).

Response to Arguments

22. Applicant's arguments filed 12/7/2010 have been fully considered.

23. With respect to the rejections under § 103, Applicant argues for the existence of unexpected results, pointing to a declaration by Dr. Struck (Reply, page 12).

The declaration under 37 CFR 1.132 filed 12/7/2010 is insufficient to overcome the rejection of claims 1-11, 16, 19-22, 25, 31, 35-37, 40-41, 45-49, 51, 55, 58, 60-63, and 68 based upon § 103 as set forth in the last Office action for the following reasons.

The Struck declaration argues that mid-proAM has unexpected stability, a property leading to unexpected advantages of the claimed methods. Specifically, the declaration states that the data reported in Applicant's postfiling publication by Morgenthaler et al. demonstrates that unlike ADM, mid-proAM is stable for at least three days (see especially the Struck declaration at the paragraph bridging pages 2-3). The Struck declaration argues that this difference in stability represents a significant advantage in comparison to the instability of ADM.

Whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007).

In addition, the burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an unexpected difference." In re Klosak, 455 F.2d 1077, 1080 (CCPA 1972). Moreover, it has been long held that "even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges 'produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." In re Huang, 100 F.3d 135, 139 (Fed. Cir. 1996)

(quoting In re Aller, 220 F.2d 454, 456 (1955), and citing In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990)).

In the instant case, it does appear based on the data presented in the Morgenthaler et al. and Lewis et al. publications that mid-proAM is more stable than ADM (although this is difficult to ascertain for certain as different researchers separately examined the stability of these peptides and it is not apparent whether this was done under similar conditions; no side-by-side comparison of the stability of mid-proAM vs. ADM has apparently been made).

However, Applicant has not shown why such a difference in stability would have been unexpected. Applicant has not satisfactorily explained why one of ordinary skill in the art would have expected these different molecules to have the same stability. Given that mid-proADM and ADM are two different peptides that differ wholly in amino acid sequence, size, chemical composition, etc., one of ordinary skill in the art would have reasonably expected these molecules to have different properties. As such, there is insufficient evidence to conclude that a difference in stability would have been unexpected.

Furthermore, the Struck declaration argues for a significant advantage for determination of mid-proAM in comparison to ADM (page 3). Such remarks are apparently premised on the idea that one would determine both mid-proAM and ADM for the same purpose; e.g. that one is determining mid-proAM as a surrogate or substitute for determining ADM. However, the claims are not limited to methods in which mid-proAM is being determined for any particular purpose.

Put another way, the asserted advantage would only be applicable for situations in which a researcher was seeking to determine mid-proAM as a replacement for an ADM assay. As such, comparing the claimed mid-proAM assay with the prior art ADM assay is inapt since the claims

encompass the determination of mid-proAM for any reason. Given that Kennedy et al. (discussed above) call for studies to define the specific role of mid-proAM, the evidence of record suggests that one of ordinary skill in the art would have been motivated to pursue detection of mid-proAM in and of itself, and not just as a substitute or surrogate for determining ADM.

Consequently, the unexpected results alleged in assaying mid-proAM vs. ADM are also not commensurate with the scope of the claims, given that the claims are not limited to the detection of mid-proAM as a substitute for detecting ADM, and as the prior art suggested the detection of mid-proAM for other reasons.

For all of these reasons, the evidence of non-obviousness fails to outweigh the evidence of obviousness.

24. With respect to the provisional obviousness-type double patenting rejections, Applicant argues that the cited applications were later-filed (Reply, page 13). However, as discussed in MPEP 804, a "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications. As the provisional double patenting rejections are not the only remaining rejections, they are therefore maintained at this time for reasons of record.

Conclusion

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

12/17/10